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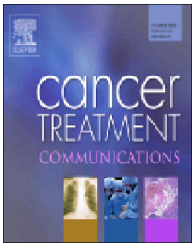

Clinicopathological features and treatment outcomes of primary thyroid lymphomas in Saudi Arabia: A case series of seven patients ☆

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Abstract
Background: Aim was to describe the clinical manifestations, diagnosis, histological types and treatment outcomes of primary thyroid lymphomas (PTLs) in Saudi population.
Materials and methods: Retrospective review of medical records of patients with thyroid carcinoma, who were treated in our center in the period from July 2005 to December 2012, was performed. Demographic, diagnostic (pathological and radiologic), histopathological and treatment parameters were collected.
Results: Among 570 records of patients with thyroid carcinoma, seven (1.23%) patients were diagnosed with PTLs. The frequent clinical presentation was a neck swelling and compression symptoms. Four (57.2%) patients were diffuse large B cell lymphomas (DLBCL); two (28.6%) patients were marginal zone B-cell mucosa-associated lymphoid tissue (MALT) lymphomas and one (14.2%) patient with T-cell lymphoma. All patients were treated with chemotherapy and involved field radiotherapy 36–40 Gy in 18–20 fractions. Median follow up was 41.6 months (12–96) with overall survival and disease free survival rates of 71.1% and 83.3%.
Conclusion: PTLs are uncommon and MALT lymphomas tend to better outcomes than other variants. However, efforts are required for incorporation of immunohistochemical methods and multimodality approach to improve the diagnosis and treatment outcomes.

Abbreviations: PTLs, primary thyroid lymphomas; CT, computed tomography; DLBCL, diffuse large B cell lymphoma; MALT, mucosa associated lymphoid tissue; HL, Hodgkin's lymphoma; TCL, T cell lymphoma; OS, overall survival; DFS, disease free survival

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1. Introduction

Primary thyroid lymphomas (PTLs) represent 2–8% of all thyroid malignancies and 1–2% of all extranodal lymphomas [1]. Thyroid gland is devoid of lymphoid tissue and PTLs are thought to develop from lymphocytes, that are acquired during the course of a chronic inflammatory or autoimmune thyroiditis (Hashimoto's disease) [2]. Most PTL are diffuse non-Hodgkin's B cell lymphoma (DLBCL), following by Hodgkin's lymphomas (HL), T cell lymphomas (TCL) and rarely marginal zone B-cell mucosa-associated lymphoid tissue (MALT) lymphomas [3].

The most common sites for extranodal DLBCL of the head and neck are Waldeyer's ring and the salivary glands. The thyroid gland is rare site and most are stage IE or IIE at diagnosis. The management of thyroid DLBCL is similar to nodal DLBCL with chemotherapy followed by radiotherapy [4].

Primary involvement of thyroid gland by HL is rare and only very few cases are reported of classical HL and nodular sclerosing subtypes and stage IIE [5].

Primary TCL are extremely rare at less than 2% of all PTLs and are diagnosed at bulky stage IE are managed with chemotherapy, radiotherapy and surgery [6].

Thyroid MALT lymphoma is one of the rare variants, which was first described by Isaacson and Wright in 1984 [7]. Primary thyroid MALT lymphomas are recognized as extranodal marginal zone B-cell lymphomas in the Revised European American Lymphoma classification of 1994 and the World Health Organization classification of 1999 [8].

Median age of presentation for PTLs is 6th and 7th decade of life and presenting complaints are generally neck swelling and compression symptoms (dysphagia or hoarseness of voice). PTLs are considered to respond better to multimodality treatments as compared to other type of lymphomas [9].

The present study aimed to evaluate the clinical, pathological, radiological and treatment outcomes of patients with PTLs in Saudi population.

2. Materials and methods

After formal approval from institutional ethical committee, medical charts of 570 patients with confirmed pathologic diagnosis of thyroid carcinoma were reviewed, who were treated in our hospital during period of July 2005 and December 2012 using computer data based system. Patients with PTLs were retrieved in the following manner:

- Demographic data (age at diagnosis, gender and symptomatology).
- Histopathological characteristics: For thyroid DCBCL and MALT lymphoma immunohistochemical positivity for CD20, CD45, CD15, and CD30 from fine needle aspiration (FNA) biopsy, core biopsy and surgery and the presence of small lymphoid cells. For T cell lymphoma, appearance of diffusely infiltrating lymphocytes with immunopositivity T-cell markers (CD3 and CD45) and for Hodgkin's lymphomas, presence of Reed Sternberg cells with immunopositivity for CD15 and CD30.
- Clinical stage, according to Musshoff's modification of Ann Arbor staging system [10] by findings from physical examination, hematological tests and electrolytes, computed tomography (CT) scan of neck, chest and bone marrow examination findings.
- Treatment modalities (surgery, chemotherapy and radiation therapy) and outcomes.
- Disease-free survival (DFS) was defined as the duration between the completion of treatment and the date of documented disease recurrence, death resulting from the cancer, and/or last follow-up visit (censored). Overall survival (OS) was defined as the duration between the completion of treatment and the date of patient death or last follow-up visit (censored).

3. Results

Among 570 diagnosed thyroid carcinoma patients, seven (1.23%) patients with PTLs were found. The patients' characteristics are listed in Table 1. Median age of patients with PTLs was 60.8 years (42–77). Six (85.7%) patients were females and one (14.3%) patient was male. Frequent presentation was rapidly enlarging neck swelling and associated compression symptoms (dysphagia or hoarseness) with or without cervical lymphadenopathy. Six patients had marked diffuse enlargement of the thyroid gland with retrosternal extension on preoperative CT neck and chest (Fig. 1). All patients had initial FNA and four patients had additional core biopsy of affected thyroid lobe for pathologic confirmation. Two patients proceeded with upfront surgery in form of thyroidectomy for confirmation of diagnosis. Among seven patients of PTLs, four (57.2%) were primary DLBCL, two (28.6%) were primary MALT lymphoma and one (14.2%) patient was with TCL (Fig. 2). Five (71.5%) patients had pathological background of Hashimoto's thyroiditis.

Patients with PTLs were treated with rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) or rituximab, cyclophosphamide, vincristine, and prednisone (R-CVP) regimen, 4–8 cycles followed by involved field radiotherapy (IFRT). Median radiation doses were between 36 and 40 Gy in 18–20 fractions using three dimensional conformal radiation therapy (3DCRT) techniques (Fig. 3).

Median follow up was 41.6 months (12–96). Primary MALT thyroid lymphomas were found to have better outcome as compared to other variants. Only one patient with DLBCL relapsed in right cheek region within 1 year of completion of treatment and was given salvage chemotherapy (patient 4 in Table 1). DFS and OS rates were 71.1% and 83.3% respectively.

4. Discussion

This is the first report of clinicopathological features and treatment outcomes of PTLs in a large cohort of thyroid carcinoma patients from Saudi Arabia. PTLs are rare with diverse clinicopathological features and treatment outcomes. PTLs were seen 1.23% of all patients with thyroid carcinoma in our study population. PTLs were seen to affect elderly females (85.7%) and in contrast to other studies from Saudi Arabia, our patients presented with an early stages [11]. Majority of patients with PTL had DLBCL variant followed by

Table 1 Patient's characteristics.

Number	Age at presentation (years)	Gender	Presentation	Type	Stage	Treatment	Radiotherapy	Status at last visit
1	60	F	Neck swelling dyspnea	DLCBL	IIE	R-CHOP × 8 cycles	36 Gy in 18 fractions	CR alive
2	42	F	Neck swelling	DLBCL	IIE	Total thyroidectomy → R-CHOP × 8 cycles	40 Gy in 20 fractions	CR alive
3	72	F	Neck swelling	DLBCL	IE	R-CHOP × 4 cycles	40 Gy in 20 fractions	CR alive
4	50	F	Neck swelling hoarseness	DLBCL	IIE	R-CHOP × 8 cycles	36 Gy in 18 fractions	Relapse dead
5	70	F	Neck swelling	MALT lymphoma	IE	RCVP × 3 → R-CHOP × 3	40 Gy in 20 fractions	CR alive
6	77	M	Neck swelling	TCL	IIE	R-CHOP × 8 cycles	40 Gy in 20 fractions	Dead
7	55	F	Neck swelling	MALT	IE	Right hemi-thyroidectomy → R-CVP × 8 cycles	40 Gy in 20 fractions	CR alive

Abbreviations: DLBCL=diffuse large B cell lymphoma, MALT=mucosa associated lymphoid tissue lymphoma, TCL=T cell lymphoma, CR=complete response, Gy=gray.

Fig. 1 Computed tomography of head and neck showing marked diffuse enlargement of the thyroid gland with retrosternal extension. The thyroid gland showing multiple large mostly ill-defined hypodense nodules those are seen mainly in the isthmus and the left lobe of the gland.

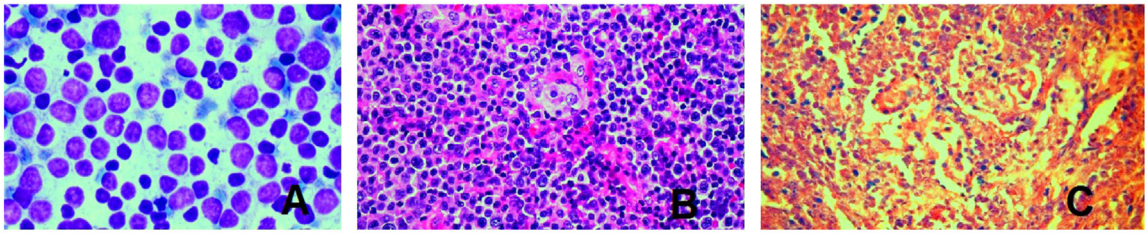

Fig. 2 Histopathological features of (A) DLBCL {presence of diffuse large B cells on Hematoxylin and Eosin staining × 200 magnification}, (B) MALT lymphoma {presence of small lymphoid cells in MALT lymphomaon Hematoxylin and Eosin staining × 200 magnification} and (C) TCL showing CD45 positivity on immunohistochemistry.

MALT lymphoma similar to other published data [2]. Furthermore, majority of our patients had background of Hashimoto's thyroiditis on pathological specimens.

PTLs were treated with multimodality approach (standard chemotherapy regimen and radiation therapy) and debulking surgery was performed for compression symptoms. However surgery should not be performed in routine in patients with PTLs without compression symptoms, as PTLs respond well with chemotherapy and radiotherapy [12].

Overall DFS (83.3%) and OS (71.1%) rates were better than other reported series. Possible explanation might be (a) early stage PTLs, (b) use of rituximab based chemotherapy and

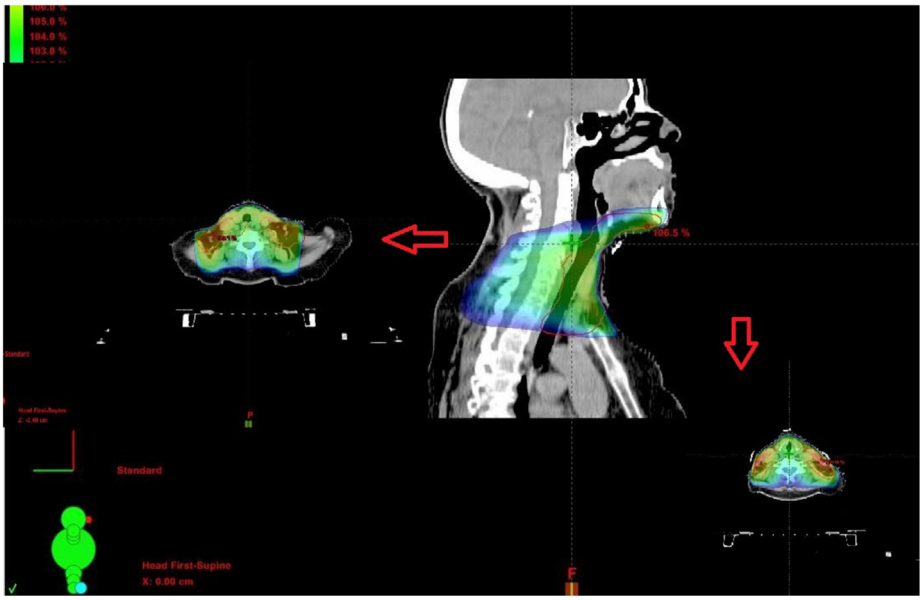

Fig. 3 Three dimensional conformal radiotherapy (3DCRT) plan of involved field radiotherapy (IFRT) showing 95% isodose distribution in axial and sagittal images.

(c) use of advanced radiation therapy techniques (3DCRT) in our patients.

In conclusion, PTLs are rare with considerable heterogeneous behavior and clinicopathologic features and treatment outcomes in Saudi population are similar to Western series. Efforts are required for the incorporation of immunohistochemical testing for prompt diagnosis and treatment.

Conflict of interest statement

No potential conflict of interest. No funds or grants were received for this study. Consents were taken from patients and relatives in case of death of patients.

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